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PATENT ABSTRACTS OF JAPAN

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(54) PERCUTANEOUS ABSORPTION TYPE ANTIINFLAMMATORY AND ANALGESIC PLASTER

(57)Abstract:
PURPOSE: To prepare a transdermal absorption type antiinflammatory analgesic plaster excellent in percutaneous absorption, reduced in physical irritation such as cuticle dissection and hair-tearing, shows systemic effect and no adverse action found in oral preparation.
CONSTITUTION: This plaster is obtained by heating and melting each component of a sticky adhesive comprising 20-60wt.% of a softener (liquid paraffin), 1-25wt.% of a tackifier (rosin), 10-50wt.% of a rubber component (styrene- isoprene-styrene block-copolymer), mixing flurbiprofen, casting on a substrate, laminating with a liner and cutting into a desired form. Flurbiprofen is an acidic non-steroidal antiinflammatory agent having a strong antiinflammatory analgesic effect and contained 40mg per sheet (136cm2, 12g). The plaster can manifest very effective antiinflammatory analgesic action even in the inflammation to which the topical application is difficult.

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* NOTICES *

CLAIMS

[Claim(s)]

[Claim 1] The percutaneous absorption type reduction-of-inflammation painkilling pasting agent which carries out the laminating of the medicine content layer containing flurbiprofen to a base material, and is characterized by the bird clapper at the binder which consists of 20 - 60 % of the weight of softeners, 1 - 25 % of the weight of tackifiers, and 10 - 50 % of the weight of rubber components.

[Claim 2] The percutaneous absorption type reduction-of-inflammation painkilling pasting agent according to claim 1 which a softener turns into from at least one sort chosen from the petroleum of paraffin series, a higher fatty acid, a polybutene, a liquefied polyisobutylene, and vegetable oil.

[Claim 3] The percutaneous absorption type reduction-of-inflammation painkilling pasting agent according to claim 1 which a tackifier becomes from at least one sort chosen from rosin, a petroleum system resin, a cumarone indene resin, a polyterpene resin, and polystyrene resin.

[Claim 4] The percutaneous absorption type reduction-of-inflammation painkilling pasting agent according to claim 1 which a rubber component becomes from at least one sort chosen from an A-B-A type tele block copolymer, natural rubber, and polyisoprene rubber.

[Translation done.]

* NOTICES *

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] this invention relates to the percutaneous absorption type resolution painkilling pasting agent which makes an active principle the flurbiprofen currently used widely in the orthopedics field as an antiphlogistic sedative drug. It is related more with a detail at the resolution painkilling pasting agent which is excellent in percutaneous absorption and has systemic action.
[0002]
[Description of the Prior Art] Recently, a non steroid anti-inflammatory agent (NSAID) is used by medication methods, such as taking orally or injection, and has the outstanding resolution analgesic action. And the part on which inflammation has generated these medicines is contacted, the dermal-administration type tablet to which a direct medicine is made to arrive at this part from the skin is developed, and Kamiichi of several sorts has already been carried out.
[0003] Thus, since the medicine by which dermal administration was carried out is absorbed from the skin without going via liver and it the dermal-administration tablet directly applied to a part not only can avoid side effects, such as digestive trouble encountered by the oral agent etc., but is absorbed by the inside of the body, without receiving decomposition by liver, a sharp reduction of the effect of a medicine is not produced. Moreover, in controlling the percutaneous absorption of a medicine, over a long time, maintenance of fixed medicine blood drug concentration is possible, and it becomes mitigable [the short time of a medicine like internal use, and the side effect which happens by extensive absorption]. moreover, even when an obstacle occurs, it is possible by removing a tablet to stop supply of a medicine immediately -- etc. -- there are the various advantages
[0004] Thus, although the dermal-administration tablet aiming at partial application had the advantage which is not in an oral agent, when the affected part was in the deep part of an organization, or when it reached far and wide, it was difficult for the affected part circumference skin to be damaged, and to have made an effect-of-a-medicine component reach the direct affected part from the skin, when application of a tablet is difficult. Therefore, it is the actual condition which cannot but use an oral agent with the danger of the side effect mentioned above since a curative effect was not demonstrated when inflammation generally crossed [rheumatoid arthritis] broadly [the affected part] moreover in a deep part, although the percutaneous absorption type tablet which is used now and developed has the comparatively small amount of percutaneous absorption of a medicine and it is effective in the disorder of ******, such as muscular pain. And as a pasting agent of the flurbiprofen which is the active principle of this invention, JP,4-173731,A and JP,6-247847,A are indicated as drainage system poultice which used the lipophilic-group agent. Moreover, JP,63-227524,A is indicated as a pasting agent using the adhesion basis of a rubber system. However, resolution analgesic action is not done so in whole body by sticking these pasting agents on a part for the partial affected part as mentioned above. Moreover, it was not what can never be satisfied also from the field of skin irritation. Therefore, the value is very large and going to just demand, if a tablet with the effect of the medicine like the whole body is developed by the percutaneous absorption type resolution painkilling pasting agent most now.

[0005]
[Problem(s) to be Solved by the Invention] Then, in order to make a medicine act in whole body by the cutaneous absorption in solving the above-mentioned technical problem, it is the first condition to pass the horny layer of the skin acting as the serious obstacle of absorption of a medicine. In order that the skin permeability of the medicine itself may conquer this condition especially in a low case, the technology which uses a penetration enhancer is required. However, these penetration enhancers also become the cause which causes skin irritation, and need sufficient cautions for the use. Moreover, in order to supply a fixed time medicine after medication, while making it a tablet not drop out from the skin in the meantime, selection of the binder which took stimulative [to the skin] into consideration enough is indispensable.
[0006]
[Means for Solving the Problem] This invention persons wholeheartedly a binder then, by specifying combination of a softener and a tackifier as a rubber component about a percutaneous absorption type resolution painkilling tablet as a result of research By making the binder of this composition contain flurbiprofen as a medicine, there was little physical irritation, such as keratin ablation and the **** hips, and it acquired the unexpected knowledge which is excellent in percutaneous absorption and discovers systemic action in the pasting agent of NSAID which only the part has expected the effect of a medicine until now. Although this knowledge showed systemic action, it came to obtain the outstanding percutaneous absorption type resolution painkilling pasting agent without the side effect that an oral agent sees.
[0007] this invention is a percutaneous absorption type resolution painkilling pasting agent which carries out the laminating of the medicine content layer containing flurbiprofen to a base material, and is characterized by the bird clapper at the binder which consists of 20 - 60 % of the weight of softeners, 1 - 25 % of the weight of tackifiers, and 10 - 50 % of the weight of rubber components.
[0008] The flurbiprofen used for this invention is 2-(2-fluoro-4-biphenylyl) propionic acid, is the acid non steroid anti-inflammatory agent which has powerful anti-inflammation and powerful analgesic action, and is matter already widely used as an internal use agent and poultice. And as an oral agent, as for the content, 40mg is used among one sheet (136cm2, 12g) as 40mg per one lock, and poultice. Also in this invention, it is an about 40mg [per sheet] content.
[0009] the rubber component used for this invention acts as an adhesion basis of the pasting agent of this invention, and its synthetic rubber, such as A-B-A type tele block copolymers, such as natural rubber, a styrene-isoprene-styrene block copolymer (SIS), and a styrene-butadiene-styrene block copolymer (SBS), and polyisoprene rubber, is independent -- or it is mixed and used The loadings are 10 - 50 % of the weight. If cohesive force will be lost if fewer than 10 % of the weight, the paste remainder arises at the time of pasting and 50 % of the weight is exceeded, it will become hard too much and an adhesive agent will be produced.
[0010] A tackifier is a resin which begins by combining with an adhesion basis and produces adhesiveness, and rosin, a petroleum system resin, a cumarone indene resin, a polyterpene resin, an alicycle group saturated-hydrocarbon resin, its rosin ester, etc. are desirable. The loadings are 1 - 25 % of the weight. If 25 % of the weight is exceeded, if fewer than 1 % of the weight, adhesive strength will be lost and it will become easy to separate, and adhesive strength is too strong, and an ache will arise at the time of ablation, ablation of a cornea layer will take place, and it will become the cause of a stimulus.
[0011] A softener demonstrates flexible physical properties with the flattery nature to the skin by carrying out dissolution softening of the adhesion basis, and blending this. As this softener, the petroleum of paraffin series, a higher fatty acid, a polybutene, a liquefied polyisobutylene, vegetable oil, etc. are desirable. The loadings are 20 - 60 % of the weight. If fewer than 20 % of the weight, the flattery nature to the skin will be lost, if 60 % of the weight is exceeded, it will become soft too much, and adhesion is lost, and the paste remainder arises at the time of pasting. Furthermore, among softeners, a liquid paraffin is the most desirable and the result

which was excellent especially from the field of the percutaneous absorption of flurbiprofen and the skin irritation of a tablet can be obtained in 40 – 50% of the weight of use.
[0012] The base material used for this invention will not be limited especially if there is no sense of incongruity when it is supple and sticks on the skin. For example, films, such as a polyolefine, polyester, polyurethane, polyvinyl alcohol, a polyvinylidene chloride, and a polyamide, or a sheet, rubber and/or a synthetic-resin nature foaming sheet, a film, a nonwoven fabric, a cheesecloth, paper, etc. are mentioned. The field of permeability to a nonwoven fabric is desirable.
[0013] In addition, to the pasting agent of this invention, perfume, such as antioxidants, such as a bulking agent used for a general pasting agent if needed and butylhydroxytoluene, an antioxidant, and peppermint oil, etc. can be added.
[0014] The manufacture method of the percutaneous absorption type resolution painkilling pasting agent of this invention is explained. After carrying out heating fusion of each component of a binder which consists of a rubber component, a softener, and a tackifier, flurbiprofen is added and it spreads to a base material, and it covers at a liner, cuts in a desired configuration, and considers as a product, or once, to a suitable base material, imprint sticking by pressure is carried out and it takes as a product after spreading the binder which contained the above-mentioned flurbiprofen on the film with which ablation processing was performed. Moreover, a binder component and flurbiprofen are scattered to solvents, such as a hexane, a heptane, ethyl acetate, and toluene, a dissolved part, and it covers at a liner after spreading dryness to the above-mentioned base material, cuts in a desired configuration, and considers as a product, or once, after spreading and dryness, imprint sticking by pressure is carried out and let the binder which contained the above-mentioned flurbiprofen on the film to which ablation processing was performed be a product at a suitable base material.
[0015]
[Function] The percutaneous absorption type resolution painkilling pasting agent of this invention has little skin irritation, and a resolution analgesic effect is acquired by the whole body like the case where taking orally is medicated, as well as the stuck part, and it can avoid the side effect generated in internal use. Therefore, partial medication can use it safely and exactly also in a difficult disorder.
[0016] An example is given to below and this invention is explained to it still more concretely.
[0017]
[Example 1] According to the loadings shown in Table 1, natural rubber was melted in toluene, a polybutene, a liquid paraffin, flurbiprofen and the peppermint oil, ARUKON P80 (an alicycle group saturated-hydrocarbon resin, product made from Arakawa Chemical industry), and butylhydroxytoluene were added to this, and the mixed dissolution was carried out. Subsequently, it dried, after spreading on a releasing paper, and the base material was stuck by pressure and imprinted on the fat dignity obtained in this way, and the pasting agent of this invention was prepared.
[0018]
[Example 2] According to the loadings shown in Table 1, the pasting agent of this invention was prepared by the same operation as an example 1 using natural rubber, SIS, a liquid paraffin, ARUKON P80, flurbiprofen, the peppermint oil, and butylhydroxytoluene.
[0019]
[Example 3] According to the loadings shown in Table 1, the pasting agent of this invention was prepared by the same operation as an example 1 using natural rubber, SIS, isobutylene isoprene rubber, a liquid paraffin, ARUKON P80, flurbiprofen, and butylhydroxytoluene.
[0020]
[Example 4] According to the loadings shown in Table 1, the pasting agent of this invention was prepared by the same operation as an example 1 using natural rubber, SIS, a liquid paraffin, rosin ester H, flurbiprofen, the peppermint oil, and butylhydroxytoluene.
[0021]
[Example 5] According to the loadings shown in Table 1, the pasting agent of this invention was prepared by the same operation as an example 1 using SIS, a liquid paraffin, a

polyisobutylene, rosin ester H, flurbiprofen, and butylhydroxytoluene.
[0022]
[Table 1]

実 施 例 の 配 合

	実施例1	実施例2	実施例3	実施例4	実施例5
天 然 ゴ ム	40	20	35	12	
S I S		20	5	20	25
流動パラフィン	21.7	49.5	42	49.5	42
ポリイソブチレン					15
ポ リ ブ テ ン	15				
ブ チ ル ゴ ム			10		
アルコンP80	20	5	5		
エステルガムH				15	15
ブチルヒドロキシトルエン	1	2	1	1	1
フルルビプロフェン	1.5	3	2	2	2
ハ ッ カ 油	0.8	0.5		0.5	

(各数値は重量部を表わす)

[0023]
[The example 1 of comparison] According to the loadings shown in Table 2, the pasting agent was prepared by the same operation as an example 1 using natural rubber, SIS, a liquid paraffin, a polybutene, rosin ester H, flurbiprofen, the peppermint oil, and butylhydroxytoluene.
[0024]
[The example 2 of comparison] According to the loadings shown in Table 2, the pasting agent was prepared by the same operation as an example 1 using an acrylic binder, flurbiprofen, and the peppermint oil.
[0025]
[Table 2]

比 較 例 の 配 合

	比較例1	比較例2
天 然 ゴ ム	35	
S I S	15	
アクリル系粘着剤		96.5
流動パラフィン	10	
ポ リ ブ テ ン	5	
エステルガムH	31.2	
ブチルヒドロキシトルエン	1.5	
フルルビプロフェン	1.5	3
ハ ッ カ 油	0.8	0.5

(各数値は重量部を表わす)

[0026] Next, the skin radiographic examination of the pasting agent of this invention, a skin stimulation test, and an effect-of-a-medicine examination are shown, and conspicuity of the effect of the pasting agent of this invention is clarified.
[0027]
[The example 1 of an examination] An exam is a skin radiographic examination. The radiographic examination was performed for the pasting agent of examples 1 and 4 and the examples 1 and 2 of comparison using the hairless-mouse extraction regions-of-back skin, and the permeability of the flurbiprofen of each sample offering pasting agent was compared.

[0028] Each sample offering pasting agent was stuck on the extraction skin, the in vitro film radiographic examination machine was equipped, the phosphate buffer solution of pH 7.4 was used for receptor liquid, and the amount of flurbiprofen which penetrates the skin and shifts into receptor liquid was measured. The result is shown in drawing 1 . The example 1 of comparison whose rosin ester H whose softeners which consist of a liquid paraffin and a polybutene are 10 % of the weight, 5 % of the weight, and a tackifier, respectively is 31.2 % of the weight had few amounts of transparency than the pasting agent of this invention the passage clear from drawing 1 . Moreover, since this has few liquid paraffins, the flattery nature to the skin is considered to be based on a bad thing. The example 2 of comparison whose binder is an acrylic binder had [else] the low permeability of flurbiprofen.
[0029]
[The example 2 of an examination] An exam is a skin-irritation examination by repetitive pasting. The pasting agent of examples 2 and 4 and the example 1 of comparison was repeated and stuck on the guinea pig, and skin irritation was compared.
[0030] Using the Hertley system guinea pig, each sample offering pasting agent was stuck on the regio lateralis which carried out depilating day for 23 hours per, and 1 hour after removal, the skin of a pasting part was observed and it judged stimulative. It was repeated for five days. In addition, the judgment was graded in accordance with the criterion of Table 3, and evaluated stimulative. The result is shown in drawing 2 . The pasting agent of this invention shows that stimulative is low compared with the example 1 of comparison with many tackifiers of a binder a passage clear from drawing 2 .
[0031]
[Table 3]

判 定 基 準

皮 膚 の 状 態	評 点
発 赤 な し	0
発赤ごく弱い（ほとんど判定困難）	1
発 赤 明 確	2
発赤中等度～強度	3
発赤きわめて強い～結痂（深達性障害）	4

[0032]
[The example 3 of an examination] An exam is an effect-of-a-medicine examination of the flurbiprofen of the pasting agent of this invention. an adjuvant arthritis rat -- receiving -- one sheet (140cm2) of example 1 prescription -- flurbiprofen 30mg -- the anti-inflammatory activity of the flurbiprofen in the internal use of the oral medicine agent which suspended the pasting agent and flurbiprofen powder to contain in gum Arabic solution 5% was measured
[0033] Adjuvant **** of the 6-weeks old male Lewis system rat was carried out, and pasting and internal use of the pasting agent (3.5cmx4cm) of an example 1 were performed for eight days from the 20-day back. Pasting of the pasting agent of an example 1 was stuck on the right hind foot day for 6 hours per, and internal use prescribed kg for the patient in 0.75mg /on the 1st. The leg edema capacity of both hind feet was measured three days after medication (23 days after ****), and after one week (27 days after ****) at the time of a medication start (20 days after ****) at the time of ****. The capacity of a foot is measured. in addition, the rate of an edema -- the rat in front of **** -- with the capacity V0 at that time (ml) Measured the capacity V1 after **** (ml), and computed the rate of an edema (%) by S=(V1-V0)/V0x100 from these values. Drawing 3 and "mean**SE" of 4 are the averages (mean), and the range which swayed to the upper and lower sides of * mark expresses the grade (SE : standard error) of dispersion in the value. * When it was presumed that there are p< 0.05, and * (p< 0.05) when it is presumed that 0.01 VS contrast authorizes statistically whether the value currently observed has a difference objective to the value of "contrast", and there is a "significant" difference and a **p< "highly significant" difference, it was marked as ** (p<

0.01), respectively. Moreover, after [1, 3, and 6] (medication one week after and 8 hours), blood was extracted and blood drug concentration was measured.
[0034] The result of the above-mentioned examination is shown in drawing 3 , 4, and drawing 5 . The pasting agent of this invention showed strong anti-inflammatory activity the passage clearer than this drawing also to the inflammation part of not only the inflammation part of the stuck right hind foot but a non-sticking left hind foot. Moreover, although just the standup of the flurbiprofen blood drug concentration after internal use was low as compared with the dermal administration of the pasting agent of this invention as shown in drawing 5 , the durability which showed high concentration and was excellent in this pasting agent also after 8 hours was expressed.
[0035]
[The example 4 of an examination] An exam is an examination of the operation to the gastric mucosa of the pasting agent of this invention. The obstacle operation in pasting and internal use of the pasting agent of an example 1 was observed to the rat gastric mucosa.
[0036] The number of the rats which cut slaughter and the stomach open and ulcer generated medication hours [6 hours] after eight days after **** in the example 3 of an examination, and the size of the ulcer were measured. The result is shown in Table 4. There were few obstacles over the stomach of the pasting agent of this invention intentionally compared with internal use.
[0037]
[Table 4]

	潰瘍の発生率	潰瘍係数(mm)
実施例1	5/10(50%)	0.85±0.34
経口投与	8/10(80%)	5.14±2.08

[0038]
[Effect of the Invention] As above-mentioned, in the pasting agent containing the flurbiprofen which is NSAID, this invention has little skin irritation and offers the useful pasting agent to which the same resolution analgesic effect like the whole body as the case where taking orally is medicated is done so, a side effect peculiar to internal use is avoided, and partial medication does effective resolution analgesic action so also in difficult inflammation.

[Translation done.]

* NOTICES *

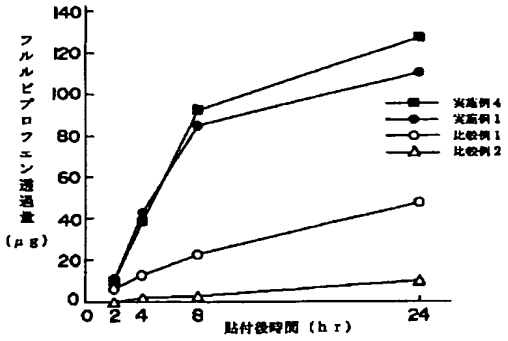
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] It is the graph which shows the radiographic examination result in the hairless-mouse skin.
[Drawing 2] It is the graph which shows the skin stimulation-test result of a guinea pig.
[Drawing 3] It is the graph which shows the anti-inflammatory activity to the leg edema of a right hind foot which stuck the pasting agent of this invention in an adjuvant arthritis rat.
[Drawing 4] It is the graph which shows the anti-inflammatory activity to the leg edema of a left hind foot which has not stuck the pasting agent of this invention in an adjuvant arthritis rat.
[Drawing 5] It is the contrast graph of the blood drug concentration after sticking the pasting agent of the flurbiprofen blood drug concentration after internal use, and this invention.

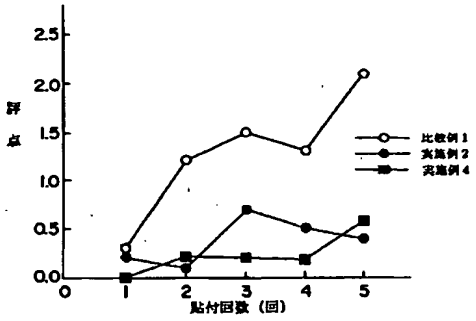
[Translation done.]

Drawing selection drawing 1



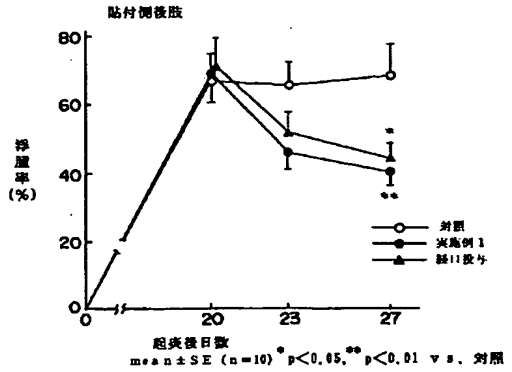
[Translation done.]

Drawing selection [drawing 2]



[Translation done.]

Drawing selection drawing 3



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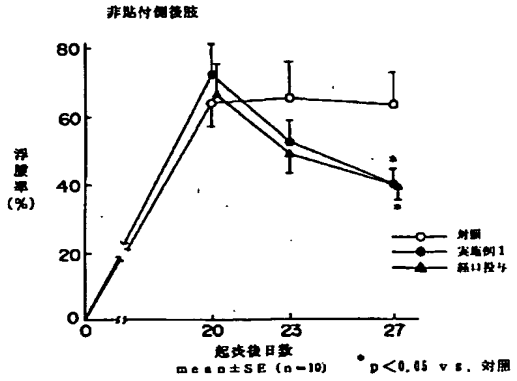
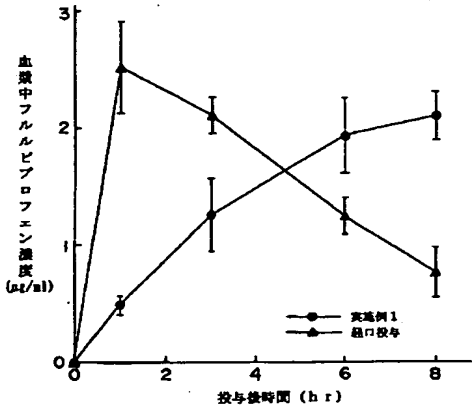


[Translation done.]

Drawing selection drawing 5



[Translation done.]